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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,693	01/29/2002	Andrew Shiau	UCAL-256/01US	9894

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EXAMINER
NASHED, NASHAAT T

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,693	SHIAU ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25,29-35 and 39-148* is/are pending in the application.

4a) Of the above claim(s) *1-25,29-35,39-43,49,51-135 and 139-141* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-48,50,136-138 and 142-148* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/21/03, 7/16/03 & 8/19/04*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The application has been amended as requested in the communication filed August 19, 2004. Accordingly, new claims 142-148 have been entered.

Applicant's election with traverse of Group V in the reply filed on August 19, 2004 is acknowledged. The traversal is on the ground(s) that Groups V and X are directed to the same subject matter and that the restriction should be made under lack of unity of invention because the instant application is a national stage application of PCT/US99/06937. Applicants' arguments are found persuasive.

The new restriction as follow:

Group I	Claims 1-25, 72-133, and 140-141, drawn to methods of identifying compounds which modulate nuclear receptor activity or modulate binding of a ligand to a nuclear receptor.
Group II	Claims 29-33, 67-71, and 134-135 drawn to a method of modulating nuclear receptor activity in a mammal.
Group III	Claims 34-35 and 39, drawn to a machine-readable storage medium capable of graphical three-dimensional representation.
Group IV	Claims 40-43, drawn to a machine-readable storage medium comprising a program for correspondence of data.
Group V	Claims 44-48, 50, 136-138, and 142-148, drawn to a crystal comprising a portion of an estrogen receptor and an agonist.
Group VI	Claims 49 and 51, drawn to a crystal comprising a portion of an estrogen receptor and an antagonist.
Group VII	Claim 139, drawn to a crystal comprising a portion of an estrogen receptor and an agonist.
Group VIII	Claims 52-66, drawn to a computational method of designing a nuclear receptor ligand.

The inventions listed as Groups I-VIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The special technical features for the inventions of Group I, III and VIII are the atomic coordinates of helix 12, whereas that of Group II is the modulator of the nuclear receptor. Although the inventions of Groups I, III and VIII share the same technical feature, they lack unity of invention because they represent more than one use of the atomic coordinates. The special technical feature for the invention of Group IV is the atomic coordinate listed in

the appendix 1 or 2. The special technical feature for the invention of Group V is the crystal comprising a protein consisting of the tripeptide Met-Asp-Pro fused to the N-terminus residues 297-554 of the human estrogen α-receptor and the agonist, whereas that of Group VI is the crystal comprising the protein-antagonist complex. Finally, the special technical feature of the invention of Group VII is the polypeptide of consisting of residue 305-549 of SEQ ID NO: 27 or SEQ ID NO: 28 which is not used to make the crystal of the ternary complex of Group V or the binary complex of Group VI.

The requirement is still deemed proper and is therefore made FINAL.

Claims 44-48, 50, 136-138, and 142-148 are under consideration.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. In particular, the application fails to comply with 37 CFR 1.821 (d), which states:

> "Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application."

The non-compliance are found through out the specification, see for example the figure description, page 10, line 26, page 11, line 31, page 13, and page 19, in particular, example 1 at page 35 line 3 and 4; and claims 46, 48, 137, 138, 142, and 143. It should be noted that the results in appendixes 1 and 2 represents a disclosure of one or more polypeptide sequence. If the amino acid sequence representing the results in the appendixes is part of the sequence listing, the heading of the Tables should identify the polypeptide(s) by sequence identification number. If the sequence is not in the sequence listing, applicants must file a new paper copy of the sequence listing contain the sequences in the Tables, and a Computer Readable Form of the sequence listing (CRF) accompanied with a statement indicating that the paper copy of the sequence listing and CRF are identical and that they contain no new matter.

The description of Figures 3A-3D and 7 indicates that the application contains color photographs. Applicants have not filed any color photograph with the application for consideration. If applicants are not intended to file color photographs, they should amend the Figure descriptions to remove any reference to color. Color photographs and color drawings are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) is granted permitting their use as acceptable drawings. In the event that applicant wishes to use the color photograph or drawings as acceptable drawings, they must file a petition for acceptance of the color photographs or color drawings as acceptable drawings. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color

photographs, as appropriate, and, unless already present, an amendment to include the following language as the first paragraph of the brief description of the drawings section of the specification:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings have been satisfied.

The disclosure is objected to because of the following informalities: The abbreviations or acronyms "OHT" and "GRIP1 NR Box II peptide" are not defined in the specification at least once, see page 11, line 10, and page 4, line 29, respectively.

Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44-48, 50, 136-138, and 142-148 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Regarding claims 44-48, 50, and 142-147, they are directed to all possible crystals of a complex of a portion of an estrogen receptor ligand binding domain, an agonist, and a molecule bound to a coactivator-binding site of said estrogen receptor. The specification, however, only provides a single representative species of these crystals in which residues the tripeptide Met-Asp-Pro, presumably, fused to the N-terminus of residue 297-554 of the human estrogen α-receptor in a complex with the agonist diethylstilbestrol and the polypeptide of SEQ ID NO: 4. Said crystal is a monoclinic crystal in space group $P2_1$ with unit cell dimension of a = 54.09 Angstrom units, b =82.22 Angstrom units, c = 58.04 Angstrom units, and β = 111.34 degrees. Moreover, the specification fails to describe additional representative species of these crystals by any identifying structural characteristics or properties other than their composition, which fails to impart a high predictability of structure for any additional crystal. Given this lack of additional representative species as encompassed by the claim, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Regarding claims 136-138 and 148, they are directed to all possible purified and isolated composition comprising an estrogen receptor ligand binding domain from any biological source, any agonist bound to the ligand binding domain and any co-activator bound to the activator binding site in solution, vapor, amorphous precipitate, or crystalline form. The specification, however, only provides a single representative species of these composition in which crystalline composition consisting of the tripeptide Met-Asp-Pro fused to the N-terminus of residue 297-554 of the human estrogen α-receptor in a complex with the agonist diethylstilbestrol, and the polypeptide of SEQ ID NO: 4. Said crystal is a monoclinic crystal in space group $P2_1$ with unit cell dimension of a = 54.09 Angstrom units, b =82.22 Angstrom units, c = 58.04 Angstrom units, and β = 111.34 degrees. Moreover, the specification fails to describe additional representative species of these compositions by any identifying structural characteristics or properties other than their composition, which fails to impart a high predictability of structure for any additional composition. Given this lack of additional representative species as encompassed by the claim, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claims 44-48, 50, 136-138, and 142-148 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature and breadth of the claimed invention encompasses any crystal of a ternary complex of any estrogen receptor-binding domain having any amino acid sequence, any agonist of said receptor bound to the ligand binding domain, and any molecule bound to a co-activator binding site. The specification provides guidance and examples in the form of an assay to express a polypeptide corresponding to residues of residues 297-554 of human estrogen α-receptor fused at the N-terminus to the tripeptide Met-Asp-Pro, purify the binary complex of said polypeptide with the agonist diethylstilbestrol, and crystallize the binary complex in the presence of the polypeptide of SEQ ID NO: 4 to obtain a monoclinic crystal in space group $P2_1$ with unit cell dimension of a = 54.09 Angstrom units, b =82.22 Angstrom units, c = 58.04 Angstrom units, and β = 111.34 degrees comprising the ternary complex under the specific crystallization conditions described on page 37, lines 4-12, see example 1. While molecular biological techniques to make any protein fragment and several crystallization methods for proteins are known in the prior ad and the skill of the artisan are developed, knowledge regarding how to obtain any protein crystal, and in particular, suitable crystal for structure determination by X-ray is lacking. Thus, searching for a crystallization conditions for any ternary complex comprising any fragment corresponding to a ligan binding domain of any estrogen receptor from any organism and having any amino acid sequence having any agonist bound in the ligand binding site, and any molecule that binds to the activator binding site to obtain any crystal, in particular, a crystal adequate

crystal for structure determination by x-ray diffraction method. The conditions of crystallization is highly dependent on the protein itself and any minor change in the amino acid sequence may require search for new crystallization conditions. It should be noted that the two crystal reported in the specification were obtained under different crystallization condition, even though the protein used for the crystallization is identical. In addition, the two crystals were different. The amount of experimentation to identify an estrogen receptor from any biological source and its ligand-binding domain, obtain adequate amount of protein, identify agonist that binds in the ligand binding site, and a molecule that binds in the activator binding site, and screen various crystallization conditions by X-ray is enormous. Producing a co-crystal of an already crystallizable protein may require searching for new crystallization conditions with no expectation of success. Since routine experimentation in the art does not include screening genomic or cDNA libraries to identify a gene encoding an estrogen receptor, identify agonist that binds to the ligand binding site or activators that bind to the activator binding site, identify the ligand binding site domain, developing a recombinant or synthetic method to make the protein, and screening for crystallization conditions, where the expectation of obtaining the desired crystal is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the chemical composition of the complex, the exact amino acid sequence of the proteins and polypeptide in the crystal, and the exact crystallization conditions. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 44-48, 50, 136-138, and 142-148 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for these rejections:

(a) The phrases "a protein of an estrogen receptor" and "binding domain" in claims 44 and 136 render the claims indefinite. For examination purposes only, the phrase "a protein of an estrogen receptor" is assumed to mean any protein or polypeptide that bind estrogen from any biological source including both the α- and β-receptors. The word domain does not identify a specific portion of a protein. For examination purposes only, the phrase is assumed to be any fragment containing the ligand-binding site of an estrogen binding protein.

(b) The phrase "derivative thereof" in claim 48 renders the claim indefinite. The phrase is not defined by the claim or the specification, and one of ordinary skills in the art would not know the metes and bound of the

claimed invention. For examination purposes only, it is assumed any chemical compound comprising the pentapeptide LXXLL (SEQ ID NO: 1) wherein X is any amino acid residue.

(c) The phrase "LXXLL" in claims 137 and 142 renders the claim indefinite. For examination purposes only, it is assumed to be "SEQ ID NO: 1".

(d) The abbreviations or acronyms "GRIP1" in claims 138 and 143, and "DES" in claim 144 and 148 are not defined at least once in the claims.

(e) Claims 45-47, 50, and 145-147 are included with these rejections because they are dependent on a rejected claim do not cure its deficiencies.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 136 and 137 are rejected under 35 U.S.C. 102(b) as being anticipated by Heery et al (IDS reference).

Heary *et al.* teach a composition comprising ternary complex consisting of a fusion protein comprising a mouse estrogen receptor ligand-binding site, residues 314-599, E2, and radiolabeled SCRC1a, see Figure 3, and the *in vitro* assay described on page 736, left column, last paragraph. The SCRC1a protein comprises several sites containing the LXXLL motif of SEQ ID NO: 1. The spots on the gels shown Figures 3a and 3b and marked GST-AFT+ correspond to the purified ternary complex consisting of GST-AF2, E2 and SRC1a. The *in vitro* assay describes a competitive assay in which a radiolabled SCRC1 and a short peptide containing the LQQLL sequence are competing to bind GST-AF2 in the presence of E2. The resulting composition is a ternary complex. The rejection is made under 102 (b) because the publication date for the prior art is June 12, 1997, and the claims are not enabled in provisional application 60/079,956, filed March 30, 1998.

Allowable Subject Matter:

Claims directed to a crystalline composition consisting of a monoclinic crystal in space group $P2_1$ consisting of the ternary complex of the polypeptide corresponding to Met-Asp-Pro fused at the N-terminus of a peptide consisting of residues 297-554 of human estrogen α-receptor, the agonist diethylstilbestrol, and the polypeptide of SEQ ID NO: 4 would be considered favorably.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nashaat T. Nashed, Ph. D.
Primary Examiner
Art Unit 1652